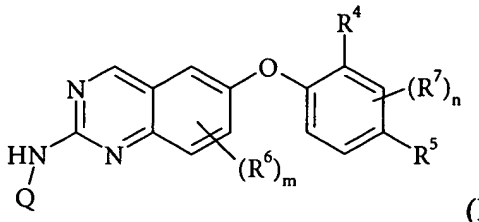
CLAIMS

The invention claimed is:

1. A compound having the Formula (I):



(I)

or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

Q is $-C(R^1R^2R^3)$;

R^1 is selected from hydrogen, alkyl, hydroxyalkyl, and alkoxyalkyl;

R^2 and R^3 are selected:

(i) independently from:

(a) hydrogen, provided if R^1 is hydrogen, only one of R^2 and R^3 may be selected from hydrogen;

(b) alkyl;

(c) alkyl substituted with one, two, or three of halogen, cyano, $-OR^8$, $-SR^8$, $-C(=O)R^8$, $-C(O)_2R^8$, $-C(=O)NR^8R^9$, $-S(O)_pR^{10}$, $-C(O)_2NR^8R^9$, - $-S(O)_2NR^8R^9$, and/or $-NR^8R^9$;

(d) $-OR^8$, $-SR^8$, $-C(=O)R^8$, $-C(O)_2R^8$, $-C(=O)NR^8R^9$, $-S(O)_pR^{10}$, $-C(O)_2NR^8R^9$, and $-S(O)_2NR^8R^9$;

(e) cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

or alternatively,

(ii) R^2 and R^3 are taken together to form an optionally-substituted cycloalkyl or heterocyclyl ring;

R^4 and R^5 are independently selected from hydrogen, halogen, cyano, haloalkyl, and haloalkoxy, provided R^4 and R^5 are not both hydrogen;

R^6 may be attached to carbon atoms C5, C7, and/or C8 of the quinazoline ring, and when attached to carbon atom C5 is lower alkyl and when attached to C7 and/or C8 is independently selected from alkyl, halogen, cyano, nitro, hydroxy, alkoxy, haloalkoxy, amino, alkylamino, and alkyl substituted with one to two of halogen, cyano, nitro, hydroxy, alkoxy, haloalkoxy, amino, and/or alkylamino;

R^7 is attached to any available carbon atom of the phenyl ring and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, cyano, nitro, hydroxy, alkoxy, haloalkoxy, amino, and alkylamino;

R^8 and R^9 are (i) independently selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; or (ii) when R^8 and R^9 are attached to the same nitrogen atom (as in $-C(O)_2NR^8R^9$, $-S(O)_2NR^8R^9$, and $-NR^8R^9$), R^8 and R^9 may be taken together to form an optionally-substituted heterocyclyl ring;

R^{10} is alkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and

p is 1 or 2.

2. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

R^1 is selected from hydrogen and C_{1-4}alkyl;

R^2 and R^3 are (i) independently selected from C_{1-6}alkyl and C_{1-6}alkyl substituted with one to two of hydroxy, $-O(C_{1-4}alkyl)$, $-C(O)_2(C_{1-4}alkyl)$, and/or $-S(O)_p(C_{1-4}alkyl)$; or (ii) R^2 and R^3 taken together form a C_{3-7}cycloalkyl or a five to six membered monocyclic heterocyclic ring, wherein each of said rings is optionally-substituted with 0 to 1 of R^{12} and/or 0 to 1 of R^{14};

R^4 and R^5 are both halogen;

R^{12} and R^{14} are independently selected from C_{1-4}alkyl, hydroxy, oxo (=O), $-O(C_{1-4}alkyl)$, $-C(=O)H$, $-C(=O)(C_{1-4}alkyl)$, $-C(O)_2H$, $-C(O)_2(C_{1-4}alkyl)$, and $-S(O)_2(C_{1-4}alkyl)$;

m is 0; and

n is 0.

3. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein R^1 is selected from hydrogen and C_{1-4}alkyl.

4. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein *m* and *n* are both 0.

5. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

R^2 and R^3 are selected

(i) independently from:

1) alkyl substituted with one or two of halogen, cyano, $-OR^8$, $-SR^8$, $-C(=O)R^8$, $-C(O)_2R^8$, $-C(=O)NR^8R^9$, $-S(O)_pR^{10}$, $-C(O)_2NR^8R^9$, $-S(O)_2NR^8R^9$, and/or $-NR^8R^9$,

2) $-S(O)_pR^{10}$, $-C(O)_2NR^8R^9$, or $-S(O)_2NR^8R^9$; and

3) cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

or alternatively,

(ii) R^2 and R^3 are taken together to form an optionally-substituted cycloalkyl or heterocyclyl ring.

6. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxy(C_{1-6}alkyl).

7. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

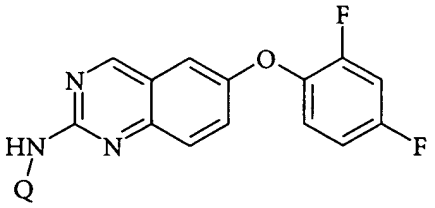
R^2 and R^3 are taken together to form an optionally-substituted C_{3-7}cycloalkyl or an optionally-substituted heterocyclic ring.

8. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

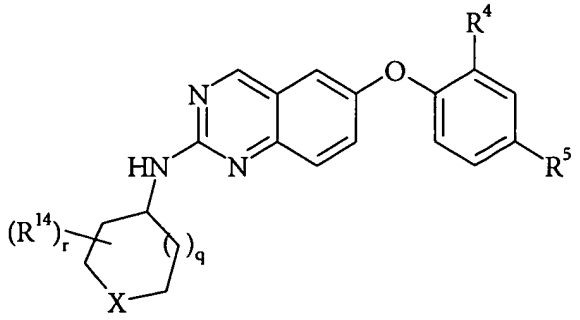
R^2 and R^3 are (i) independently selected from hydrogen, C_{1-4}alkyl, and hydroxy(C_{1-4}alkyl), provided R^2 and R^3 are not both hydrogen; or (ii) R^2 and R^3 are taken together to form cyclohexyl, piperidin-4-yl, or tetrahydropyran-4-yl, wherein each of said rings formed by R^2 and R^3 taken together is optionally-substituted with up to two of lower alkyl, –OH, $-C(O)_2(C_{1-4}alkyl)$ and/or $-S(O)_2(CH_3)$.

9. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein R^4 and R^5 are both halogen.

10. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, having the formula:



11. A compound according to claim 1, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, having the formula:



wherein:

X is –O–, –C(=O)–, –N(R^{12a})–, or –CH(R^{12b})–;

R^{12a} is selected from hydrogen, C_{1-4}alkyl, –C(=O)R^{15}, –C(O)$_2R^{15}$, and –S(O)$_2$(C_{1-4}alkyl);

R^{12b} is selected from hydrogen, C_{1-4}alkyl, –OR^{15}, –C(=O)R^{15}, –C(O)$_2R^{15}$, and –S(O)$_2$(C_{1-4}alkyl);

R^{14} is selected from C_{1-4}alkyl, oxo (=O), –OR^{15}, –C(=O)R^{15}, –C(O)$_2R^{15}$, and –S(O)$_2$(C_{1-4}alkyl);

R^{15} at each occurrence is independently selected from hydrogen and C_{1-4}alkyl;

q is 0 or 1; and

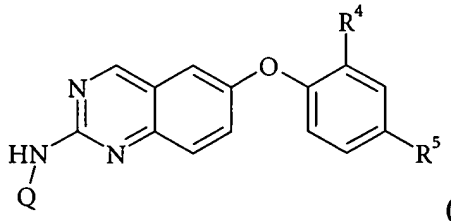
r is 0, 1, or 2.

12. A compound according to claim 11, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

R^4 and R^5 are both fluoro.

13. A compound according to claim 11, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein X is –NR^{12a}–, R^{12a} is -S(O)$_2$(C_{1-4}alkyl), and *q* is 1.

14. A compound having the Formula (Ip),



(Ip)

or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

Q is –C($R^1R^2R^3$) or an optionally-substituted cycloalkyl or heterocyclyl;

R^1 is selected from hydrogen and alkyl;

R^2 and R^3 are independently selected from –Y-R^8, –Y-OR^8, –Y–SR^8, –Y–S(O)$_p$$R^{10}$, –Y–C(=O)$R^8$, and –Y–C(O)$_2R^8$, wherein Y is C_{1-6}alkylene;

R^4 and R^5 are both halogen;

R^8 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, provided R^8 is not arylalkyl or heteroarylalkyl;

R^{10} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl, provided R^{10} is not arylalkyl or heteroarylalkyl; and

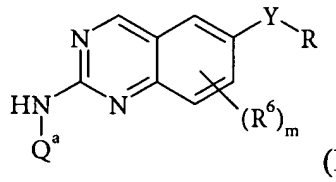
p is 1 or 2.

15. A compound according to claim 14, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein R^4 and R^5 are both fluoro.

16. A compound according to claim 14, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein at least one of R^2 and R^3 is selected from $-Y-OR^8$, $-Y-S(O)_pR^{10}$, $-Y-C(=O)R^8$, and $-Y-C(O)_2R^8$, wherein Y is C_{1-4}alkylene.

17. A compound according to claim 14, or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein Q is an optionally-substituted monocyclic cycloalkyl or heterocyclyl ring.

18. A method for treating a p38-mediated disorder in a patient comprising administering to the patient in need of such treatment, an effective amount of a compound having the formula (II):



(II)

or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

Q^a is selected from alkyl, substituted alkyl, heteroalkyl, or an optionally-substituted cycloalkyl or heterocyclic ring, provided that Q is not arylalkyl or heteroarylalkyl;

Y is –O–, –S–, or –NR' –, wherein R' is hydrogen, lower alkyl, or lower alkyl substituted with OH;

R is alkyl, substituted alkyl, or optionally-substituted aryl, heteroaryl, cycloalkyl, or heterocyclyl;

R^6 is attached to any available carbon atom of the quinazoline ring and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, cyano, nitro, hydroxy,

alkoxy, haloalkoxy, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

m is 0, 1, 2 or 3.

19. The method of claim 18, comprising administering to the patient an effective amount of a compound having the formula (II), or an isomer, prodrug, or pharmaceutically-acceptable salt thereof, wherein:

Y is –O–;

R is C_{1-6}alkyl or phenyl optionally-substituted with one to two groups selected halogen, haloalkyl, and haloalkoxy;

Q is selected from (i) C_{1-6}alkyl, (ii) C_{1-6}alkyl substituted with one to two groups selected from hydroxy, –O(C_{1-4}alkyl), –S(=O)(C_{1-4}alkyl), –S(O)$_2$(C_{1-4}alkyl), and/or –C(O)$_2$(C_{1-4}alkyl); or (iii) cyclohexyl, piperidinyl, or tetrahydropyranyl, wherein each of said rings is optionally substituted with one of OH, –C(O)$_2$(C_{1-4}alkyl) or –S(O)$_2$(C_{1-4}alkyl); and

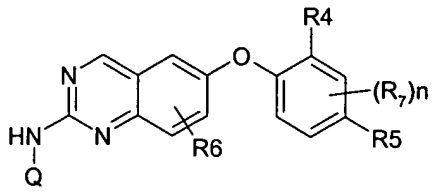
m is 0.

20. A pharmaceutical composition comprising a therapeutically effective amount of compound according to Claim 1 in combination with a pharmaceutically-acceptable excipient.

21. A method for treating a p38-mediated disorder in a patient comprising administering to the patient in need of such treatment, an effective amount of a compound according to Claim 1.

22. The method of Claim 21, wherein the p38-mediated disorder is selected from the group consisting of arthritis, Crohn's disease, Alzeihmer's disease, adult respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, stroke, sepsis, myocardial infarction, and spondylitis.

23. A process for preparing a compound of formula (I)



wherein Q is $-C(R^1R^2R^3)$;

R^1 is selected from hydrogen, alkyl, hydroxyalkyl, and alkoxyalkyl;

R^2 and R^3 are each independently hydrogen, provided if R^1 is hydrogen, only one of R^2 and R^3 may be selected from hydrogen; alkyl; alkyl substituted with one, two, or three of halogen, cyano, $-OR^8$, $-SR^8$, $-C(=O)R^8$, $-CO_2R^8$, $-C(=O)NR^8R^9$, $-S(O)_pR^{10}$, $-CO_2NR^8R^9$, $--SO_2NR^8R^9$, and/or $-NR^8R^9$; $-OR^8$, $-SR^8$, $-C(=O)R^8$, $-CO_2R^8$, $-C(=O)NR^8R^9$, $-SO_pR^{10}$, $-CO_2NR^8R^9$, and $-SO_2NR^8R^9$; cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; or alternatively R^2 and R^3 are taken together to form an optionally-substituted cycloalkyl or heterocyclyl ring;

R^4 and R^5 are independently selected from hydrogen, halogen, cyano, haloalkyl, and haloalkoxy, provided R^4 and R^5 are not both hydrogen;

R^6 may be attached to carbon atoms C5, C7, and/or C8 of the quinazoline ring, and when attached to carbon atom C5 is lower alkyl and when attached to C7 and/or C8 is independently selected from alkyl, halogen, cyano, nitro, hydroxy, alkoxy, haloalkoxy, amino, alkylamino, and alkyl substituted with one to two of halogen, cyano, nitro, hydroxy, alkoxy, haloalkoxy, amino, and/or alkylamino;

R^7 is attached to any available carbon atom of the phenyl ring and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, cyano, nitro, hydroxy, alkoxy, haloalkoxy, amino, and alkylamino;

R^8 and R^9 are (i) independently selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; or (ii) when R^8 and R^9 are attached to the same nitrogen atom (as in $-C(O)_2NR^8R^9$, $-S(O)_2NR^8R^9$, and $-NR^8R^9$), R^8 and R^9 may be taken together to form an optionally-substituted heterocyclyl ring;

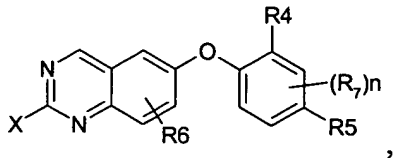
R^{10} is alkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and

p is 1 or 2; wherein said process comprises:

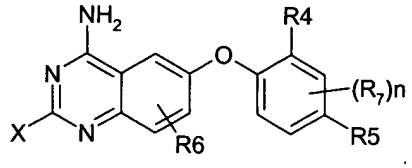
(i) providing a compound of formula (10)



, wherein X is a leaving group; and

(ii) contacting said compound of formula (10) with a compound of the formula Q-NH_2.

24. The process of claim 23, wherein said compound of formula (10) is provided by contacting a compound of formula (9) with t-butyl nitrite:



* * * * * * * * *